Section II. REMARKS

The pending claims are 1-9, 11 and 13-20.

Restriction/Election

It is noted that the Examiner indicated in the September 1, 2009 Office Action that the applicants' argument in response to the restriction requirement was "not found persuasive," however, the Examiner then indicated that the "restriction requirement has been withdrawn." Applicants request that the Examiner acknowledge that the arguments presented by applicants were persuasive, which was why the restriction requirement was withdrawn.

Amendments to the Claims

Support for the amendment to claim 1 regarding the cytochrome P450 reductase can be found in the instant specification at page 8, lines 7-12.

No new matter has been added herein.

Objections to the Claims

In the September 1, 2009 Office Action, the Examiner objected to claims 2-8 and 14-20 because of grammatical informalities. Applicants have corrected the grammatical issues in said claims, thereby obviating the objections. Withdrawal of same is respectfully requested.

Rejection of Claims and Transversal Thereof

In the September 1, 2009 Office Action:

claim 13 was rejected under 35 U.S.C. §102(b) as being anticipated by Brimer et al. (Pharmaceutical Research 2000 United States, 17(7), 803-810 (2000));

claims 1-9, 11, and 13-20 were rejected under 35 U.S.C. §103(a) as being unpatentable over Bort et al. (*Biochem. Pharmacol.*, 58(5), 787-796 (1999)) in view of Gómez-Lechón et al. (*Curr. Drug Metabolism*, 4(4), 292-312 (2003)); and

claims 1-8 and 13 were rejected under 35 U.S.C. §112, second paragraph.

These rejections are respectfully traversed. The patentable distinctions of the pending claims over the cited references are set out in the ensuing discussion.

Rejection under 35 U.S.C. §102

In the September 1, 2009 Office Action, claim 13 was rejected under 35 U.S.C. §102(b) as being anticipated by Brimer et al. (*Pharmaceutical Research*, 17(7), 803-810 (2000)) (hereinafter Brimer). Applicants traverse such rejection.

Claim 13 has been amended to recite:

> **13. A method to confer to a cell line expressing cytochrome P450 reductase the capacity to metabolize xenobiotics in a controllable manner, said method comprising the transfection of said cell line with a set of more than one adenoviral expression vectors, wherein each expression vector comprises an ectopic DNA sequence coding for a CYP450 enzyme involved in xenobiotic biotransformation and wherein each of the CYP450 enzymes are different.**

The Examiner has indicated that Brimer discloses transfecting Caco and LLC-PK1 cells with adenoviral vectors expressing CYP3A4 and NADPH P450 reductase, which is a Phase I enzyme and a cytochrome P450 reductase, respectively.

Comparing Brimer with claim 13 as presently pending, it can be seen that claim 13 requires the transfection of the cell line with a set of more than one adenoviral expression vectors, wherein each expression vector codes a CYP450 enzyme, wherein each of the CYP450 enzymes are different. In contrast, Brimer discloses a cell line that only expresses one CYP enzyme (i.e., CYP3A4).

It is well established, as a matter of law, that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Clearly, Brimer does not satisfy this standard.

Withdrawal of the rejection of claim 13 under 35 U.S.C. §102 is respectfully requested.

Rejection under 35 U.S.C. §103(a)

In the September 1, 2009 Office Action, claims 1-9, 11, and 13-20 were rejected under 35 U.S.C. §103(a) as being unpatentable over Bort et al. (*Biochem. Pharmacol.*, 58(5), 787-796 (1999)) (hereinafter Bort) in view of Gómez-Lechón et al. (*Curr. Drug Metabolism*, 4(4), 292-312 (2003)) (hereinafter Gómez-Lechón). Applicants traverse such rejection.

According to the Examiner, Gómez-Lechón does not teach "transfecting multiple adenoviral vector [sic] that expresses [sic] different phase I or phase II enzyme to cells of hepatic origin" but Bort demonstrated that it is feasible to use hepatic cell lines expressing single CYP enzymes. The Examiner went on to state that "[s]ince Gómez-Lechón [Bort?] taught the limitation of cell line expressing single CYP, an ordinary [person] skilled in the art would have been motivated to modify such system by introducing additional Phase I or Phase II enzymes such that the cell line will reflect the whole spectrum of human xenobiotic metabolizing enzyme expression profile." Applicants vigorously disagree.

Gómez-Lechón relates to the use of human hepatocytes as a tool for studying toxicity and drug metabolism. Specifically, Gómez-Lechón analyzes the differential changes in expression and activity of different CYP isoforms in response to different xenobiotics and suggests the use of adenoviral vectors that allows the simultaneous expression of multiple genes as well as the modulation of the level of the transgenes expression. However, this suggestion is made only in the context of regulating the expression of CYP isoforms by modulating the activity of a family of transcription factors known as liver-enriched and ubiquitous regulatory factors transcription factors (the so-called LEFTs) specific for each of said CYP isoforms.

In contrast, the method defined in claim 1 differs from the method described by Gómez-Lechón in that applicants' claimed Phase I and Phase II enzymes are expressed in the cells, not by increasing the expression of the transcription factors (i.e., the so-called LEFTs) disclosed in Gómez-Lechón, but instead by expressing the enzymes using a set of more than one recombinant adenoviral expression vectors comprising an ectopic DNA sequence that codes for a different phase I or phase II enzyme. Moreover, there is no motivation in Gómez-Lechón to express enzymes using a set of more than one recombinant adenoviral expression vectors comprising an ectopic DNA sequence that codes for a different phase I or phase II enzyme. Applicants' claimed method allows for the regulation of the

expression levels of the enzyme since there is a correlation between the dosage of adenoviral particles and the expression level of the enzyme encoded by the corresponding adenovirus.

Bort describes epithelial cells genetically modified so that they express a unique human CYP (Phase I enzyme). These cells have been obtained by transfection with a plasmid vector wherein the CYP-encoding cDNA is under the control of the CMV promoter. Bort does not mention the possibility of using a set of more than one recombinant adenoviral vectors, or of coding for a different phase I or phase II biotransformation enzyme, as claimed by applicants herein.

Considered in combination, as proposed by the Examiner, the contents of Bort would not have prompted one of ordinary skills in the art to modify the cell model disclosed in Gómez-Lechón so as to incorporate additional phase I or II biotransformation enzymes, let alone to incorporate these additional enzymes by the use of adenoviral vectors when attempting to achieve a controlled expression of the metabolic enzymes, since the advantage of using the adenoviral vectors was not disclosed in either Gómez-Lechón nor Bort.

Further, just because Gómez-Lechón, in the words of the Examiner, "established that there is a need for such engineered cell line to be made for the purpose of studying drug metabolism," does not mean that the process of achieving same is obvious. It is well settled in the law that an obviousness rejection cannot be predicated on that which is unknown. *In re Spormann*, 150 U.S.P.Q. 449, 452 (CCPA 1966). Thus, the subject-matter of claim 1, and the claims that depend therefrom, is not obvious in view of Gómez-Lechón in combination with Bort.

Claims 9 and 13 contain similar limitations to claim 1 and as such, said claims, and the claims depending therefrom, are non-obvious in view of Gómez-Lechón in combination with Bort.

Rejection under 35 U.S.C. §112

In the September 1, 2009 Office Action, claims 1-8 and 13 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Applicants traverse such rejection.

Regarding claim 1, the Examiner considered that the recitation "to obtain expression vector cells that transitorily express said ectopic DNA sequences and present a different phenotypic profile of Phase I or Phase II drug biotransformation enzymes" renders the claim indefinite because it is unclear how the

expression vector and or cells are obtained in the context of the claim. Moreover, the recitation of "a singular cell model ... wherein said model..." also renders the claim indefinite because it is unclear whether said cell model comprises a set of vectors, a single cell, or multiple cells.

Applicants have amended claim 1 to replace the phrase "to obtain expression vector cells that transitorily express said ectopic DNA sequences and present a different phenotypic profile of Phase I or Phase II drug biotransformation enzymes" with "to obtain cells that transitorily express said ectopic DNA sequences," thereby overcoming this rejection. Further, the word "singular" has been removed to avoid the second §112 rejection on claim 1.

Regarding claim 13, the Examiner indicated that the phrase "a set of more than one adenoviral vectors selected from the group consisting of Phase I enzymes, Phase II enzymes and cytochrome P450 reductase" renders the claim indefinite because none of the enzyme from the group is an adenoviral vector. Applicants have amended claim 13, which should be clear.

Thus, it is submitted that claims 1 and 13 are no longer indefinite and thus, they comply with the requirements of 35 U.S.C. § 112.

Conclusion

The pending claims are in form and condition for allowance. Authorization is hereby given to charge any deficiency in applicable fees for this response to Deposit Account No. 13-4365 of Moore & Van Allen PLLC. If any additional issues remain, the Examiner is requested to contact the undersigned attorney at (919) 286-8000 to discuss same.

Respectfully submitted,

MOORE & VAN ALLEN PLLC

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By: _____

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